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Calcium-containing renal stones

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The majority of stones that form within the urinary tract contain calcium, and various crystalline forms of calcium oxalate and calcium phosphate are the types of stones most often found [1,2]. These urinary tract calculi are not the disease but simply an expression of varied metabolic disorders that produce stones of similar crystalline composition; thus, in evaluating a patient in whom a calcium-containing stone has developed, it is important for the physician to consider the possible conditions that may have led to this complication [3]. Outlined in Table 1 is an etiologic classification of calcium urolithiasis. Before considering special features of these metabolic disorders, it is helpful to review the general medical evaluation of patients who have calcium-containing renal stones.

General medical evaluation

The medical evaluation of a patient with calcium urolithiasis includes consideration of the historical aspects of the disorder, assessment of the metabolic activity of the stone formation, and performance of laboratory studies to define the specific cause of the stone formation. Although these factors overlap, it is helpful to consider them first as independent elements of the medical evaluation and then to discuss their interrelationships in the diagnosis of the patient with calcium urolithiasis.

A number of features in the medical history should be considered (Table 2). The patient's age at the onset of the problem may help direct the evaluation. Primary hyperoxaluria, renal tubular acidosis, and cystinuria commonly occur before puberty. The peak age at onset for primary hyperparathyroidism is in the sixth decade and for idiopathic urolithiasis, in the fourth decade. Idiopathic urolithiasis is much more common in males than in females, with a ratio of approximately 5:1. Primary hyperparathyroidism occurs more commonly in females than in males, with an approximate ratio of 2:1. A family history of urolithiasis is often present in patients who have inherited disorders of metabolism. In the syndrome of idiopathic urolithiasis, which includes varied metabolic disorders, a family history of stones is also common, but because of the heterogeneous nature of the metabolic abnormalities that may be found in these patients, the patterns of inheritance have not been established.

Dietary factors in the medical history that may be helpful include fluid intake and an estimation of the dietary intake of calcium and oxalate. Medication such as absorbable alkali, vitamin D, and carbonic anhydrase inhibitors can promote the complications of urolithiasis and nephrocalcinosis; therefore, a careful history of drug ingestion should be taken. Proprietary drugs containing calcium carbonate and sodium bicarbonate may often be overlooked. Residence in geographic areas where urolithiasis is known to be especially frequent may be an additional consideration in the medical history of some patients.

The physical appearance of stones passed or removed surgically may provide clues to their composition. The patients may know the results of previous stone analyses or they may have saved a stone. If so, the stone should be obtained and analyzed. Knowledge of its composition is especially helpful in recognizing patients with cystinuria, uric acid lithiasis, and the secondary conditions producing struvite (magnesium-ammonium-phosphate) stones.

The pattern of the complications with stones should be documented in each patient. Colic, hematuria, passage of stones and gravel, obstruction, and surgical manipulations are all important elements in the medical history. Documented infection and its associated symptoms should be recorded. If the patient can recall the types of bacteria present in the urine, additional insight into the current problem may be gained (see Dr. Griffith's article, this issue). The recurring presence of *Proteus* species in the bladder urine suggests infected urolithiasis. It is im-

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Table 1. Calcium urolithiasis

I. Renal tubular acidosis
A. Type I distal tubular defect
B. Carbonic anhydrase inhibitors
II. Hyperoxaluric states
A. Primary hyperoxaluria
1. Type I—glycolic aciduria
2. Type II—L-glyceric aciduria
B. Enteric (acquired) hyperoxaluria
III. Hypercalcemic states
A. Primary hyperparathyroidism
B. Immobilization
C. Sarcoidosis
D. Hypervitaminosis D
E. Milk-alkali syndrome
F. Neoplastic disorders
G. Cushing's syndrome
H. Hyperthyroidism
I. Others
IV. Idiopathic renal lithiasis
V. Secondary urolithiasis
A. Infected urolithiasis
B. Obstructive urolithiasis

portant to remember that all too often the presence of white blood cells (pus) in the urine has led to a diagnosis of infection and that antimicrobials may have been given without actual demonstration of infection by culture. Commonly, patients with stones in the upper urinary tract will have both pyuria and hematuria without associated bacteriuria.

There are a number of other medical disorders that should be sought in the medical history because they relate to the formation of stones within the urinary tract. Conditions associated with hypercalcemia and hypercalciuria may be complicated by calcium urolithiasis (Table 1). The one exception is the hypercalcemia of malignancy, in which stone formation is distinctly rare, perhaps because the hypercalcemia often heralds the terminal phase of the disease and is thus of short duration. In patients with gastrointestinal disease, especially after bowel surgery, stone formation may occur (see Dr. Williams's article, this issue). Peptic ulcer disease or pancreatitis may have been the presenting sign of primary hyperparathyroidism. Symptoms of dyspepsia, heartburn, or ulcers may have been treated with absorbable alkali and milk, and patients with glaucoma may have been treated with carbonic anhydrase inhibitors; both of these situations would increase the tendency to the formation of stones.

Table 2. Features of the medical history in the evaluation of calcium urolithiasis

I. Age at onset
II. Sex
III. Family history
IV. Diet and drug history
V. Geographic residence
VI. Clinical considerations
A. Nature of stones
B. Stone history
C. History of urinary tract infection
D. Other medical disorders and surgery
E. Previous roentgenograms

Previous roentgenograms may be available with which to assess the nature of the stone formation and to help in determining its progression. As will be discussed subsequently, such X-ray films are vital in determining the metabolic activity of the stones.

A major problem in evaluating a patient with calcium urolithiasis relates to the metabolic activity of the stone formation. Irrespective of the underlying cause, stone formation varies among patients with the same disorder. Some patients are constantly forming stones and other patients do not form stones at all, and between these extremes is a full spectrum of variations. An excellent example of this is primary hyperparathyroidism, in which no more than 50% of the patients with surgically proven hyperparathyroidism have ever had a stone [4]. For this reason, it is extremely important to establish criteria for metabolic activity if one is to use long-term therapy appropriately for those patients who are actively forming stones and who therefore need it.

We established arbitrary criteria of the activity of stone formation in 1965 when our Stone and Parathyroid Clinics were established [5]. "Surgical activity" is said to be present when the patient has colic, obstruction, or infection associated with a stone which often requires surgical intervention. This in itself does not imply metabolic activity, because the stone causing the trouble may have been formed long before, without there having been any subsequent change in size.

"Metabolically active urolithiasis" is considered to be present when one or more of the following criteria are satisfied: *1)* roentgenographic evidence of new stone formation within the past year, *2)* roentgenographic evidence of stone growth within the past year, or *3)* the passage of documented gravel within the past year. If none of these criteria is present and previous roentgenograms are adequate, then the stone formation is considered "inactive" and the patient is managed by a high fluid intake and periodic follow-up. If infected or obstructive urolithiasis is present, the metabolic activity cannot be evaluated until this secondary problem has been eliminated.

When previous roentgenograms are not available or are inadequate for evaluation of the activity of the stone formation, a category of "indeterminate metabolic activity" is assigned. These patients are carefully instructed with regard to a high fluid intake and dietary restriction when indicated, and they are followed periodically with roentgenograms (plain film

with tomographic views) until a classification of the metabolic activity can be made. In the follow-up (mean of eight years) of 101 consecutive patients with idiopathic urolithiasis in whom the metabolic activity of the stone formation was initially termed "indeterminate," 64 patients (63%) were found to have "metabolically inactive urolithiasis" on the conservative treatment program [3]. Had these patients been started on specific therapy without establishment of the need for it, approximately two-thirds of the patients would have been committed to unnecessary life-long therapy.

There are obvious limitations to this classification of metabolic activity. First, the evaluation is limited to the resolution obtained on roentgenograms. Although this resolution has been improved by the use of tomography, there remains a minimum stone size (no less than approximately 1 mm) that can be identified, and this is influenced by the density of the stone. Second, if the stone moves and reorients its axis, its size may falsely appear to have changed because of its irregular shape. Third, and perhaps most important, the complication of new stone formation or growth must occur before therapy has been instituted. In spite of these limitations, the clinical criteria of metabolic activity have been very useful in helping us to restrict specific therapy to those patients who need it.

The laboratory evaluation of the patient with calcium urolithiasis should be influenced by the medical history and the preliminary assessment of metabolic activity. Since continued follow-up of the patient with urolithiasis is the cornerstone to successful management, the laboratory evaluation of the patient often can proceed stepwise. Outlined in Table 3 is the general laboratory evaluation we use in patients with calcium urolithiasis. To this, special tests are added to define specific metabolic disorders when indicated. The list of tests is long and many of them are costly, and for this reason we believe that it is extremely important to approach each patient individually and not to establish a "routine" for all patients seen for evaluation of calcium urolithiasis. For instance, the laboratory evaluation of an asymptomatic 60-yr-old man whose three stones have not changed on roentgenograms over the past five years might include serum calcium, phosphorus, uric acid, and creatinine determinations, urinalysis, and urine culture. If these studies are normal or negative, then regular follow-up of his urolithiasis can be done at the time of his annual medical examination. Additional studies would be indicated only if there was a change in the status of the activity of his stone formation.

These general considerations in the medical evaluation of the patient with calcium urolithiasis can be applied now to the metabolic disorders listed in Table 1 and can be made more specific for each of these disorders. Hyperoxaluria (see Dr. Williams's article, this issue) and secondary urolithiasis (see Dr. Griffith's article, this issue) have been discussed elsewhere in this symposium and will not be considered further.

Table 3. Laboratory evaluation of calcium urolithiasis

I.	Serum
	Calcium × 3
	Phosphorus
	Uric acid
	Creatinine/blood urea nitrogen
	Alkaline phosphatase
	Protein electrophoresis
	Immunoreactive parathyroid hormone
II.	Urine
	Urinalysis
	Urine culture and sensitivity
	Urinary pH (fasting state)
III.	Urine chemistry (24-hr collection)
	Calcium
	Phosphorus
	Uric acid
	Oxalate
	Cystine
	Creatinine
IV.	Renal function
	Creatinine clearance (inulin and PAH clearance)
V.	Roentgenograms
VI.	Stone analysis (if available)

Renal tubular acidosis

Renal tubular acidosis (RTA) is associated with disturbances in acid-base balance by the kidney [6,7]. Type I RTA is characterized by an inability of the distal nephron to generate or maintain steep luminal-peritubular hydrogen ion gradients. In this condition, conservation of bicarbonate and production of ammonia are usually normal. The patient is unable to excrete urine of a pH less than 5.8, even in the presence of systemic acidosis. Hyperchloremic acidosis, hypokalemia, and urinary wasting of sodium, potassium, calcium, and phosphorus occur. Calcium urolithiasis, nephrocalcinosis, muscle weakness, and osteomalacia may develop.

Type II RTA is associated with a proximal renal tubular defect in reabsorption of bicarbonate without the distal tubular abnormalities. To date, urolithiasis and nephrocalcinosis have not occurred with Type II RTA.

Both defects have been reported in a few patients. RTA may be transmitted as an autosomal-dominant pattern of inheritance. More commonly, it occurs spontaneously or in association with systemic diseases.

The diagnosis of type I RTA is made by demonstrating an inability to acidify urine below a pH of 5.8

in the presence of systemic acidosis and in the absence of abnormalities in metabolism of bicarbonate and ammonia by the kidney. Measurement of the pH (with a pH meter) of the second voided morning urine after the patient has fasted overnight provides a simple method for screening patients with calcium urolithiasis. If the urinary pH is not less than 5.5, a solution of ammonium chloride (500 mg/5 ml) is given orally at a dosage of 100 mg/kg per 24 hr. Bicarbonate and pH are measured in the plasma and urine. If the urinary pH remains above 5.8 when the plasma bicarbonate concentration decreases below 20 mEq/liter in the absence of a renal leak of bicarbonate, the diagnosis of type I RTA is confirmed, and the administration of ammonium chloride is stopped. Because bacterial metabolism may alter urinary pH, measurement of urinary pH must be done only after it has been shown by culture that the patient is free of bacteriuria.

Treatment of patients with type I RTA involves correction of their metabolic abnormalities. Replacement of sodium, potassium, and base is usually required. It is important to remember that with significant systemic acidosis, serum potassium may be normal in spite of a major deficit in total body potassium. Replacement of base alone in this setting may be lethal. Base requirements usually range from 60 to 120 mEq per day and should be given in divided doses either as sodium bicarbonate or as citrate solution. Serum potassium should be monitored carefully, and replacement should be provided as needed. The stone formation and nephrocalcinosis in some of these patients will be arrested with this replacement program. When stone formation and nephrocalcinosis have progressed in spite of adequate metabolic replacement therapy, oral orthophosphate has been used effectively [8].

Carbonic anhydrase inhibitors, which are used primarily in patients with glaucoma, can produce abnormalities in acid-base metabolism in the kidney [9]. In a small number of these patients, calcium urolithiasis will develop. In our experience, patients in whom this complication develops have often, but not always, a past history of stone formation that was inactive until the medication was started. Stopping use of the carbonic anhydrase inhibitor, if possible, will usually arrest the stone formation; if this is not possible, oral orthophosphate has been used effectively to prevent further stone formation [8].

Hypercalcemic states

Included in Table 1 are some of the disorders that can cause hypercalcemia and be associated with urolithiasis. The initial step in recognizing this complication of those metabolic disorders is the identification of increased serum concentration of calcium. Stated normal ranges in healthy subjects have varied widely, even when the same method of chemical analysis has been employed. A range of serum calcium of 9 to 11 mg/dl, which has been commonly used in the past as the normal range, would not have led to the diagnosis of hypercalcemia in 31% of the patients in one series who had surgically documented primary hyperparathyroidism with complications of their disease [4]. In our laboratory, the normal range of serum calcium is 8.9 to 10.1 mg/dl, which was established by the careful studies by Keating et al [10]. The normal range may vary, depending on the method of chemical analysis, but it should be established within each clinical laboratory. Serum protein content will affect the protein-bound fraction of calcium within the serum; therefore, it is also important to measure serum concentration of proteins when evaluating that of serum. Ideally, three or more serial serum calcium determinations are used to establish the presence of hypercalcemia.

Hypercalciuria (greater than 300 mg of calcium in the urine per 24 hr when on a normal calcium intake) usually accompanies hypercalcemia and has been thought to be important in the formation of stones within the urinary tract. This hypercalciuria may be masked if there is significant impairment of renal function (a GFR of less than 30 ml/min). Hypercalciuria may not be present in some patients with primary hyperparathyroidism when the effect of parathyroid hormone in increasing the tubular reabsorption of calcium is greater than the effect of hypercalcemia in increasing the filtered load of calcium in the glomerulus. The most common crystal system occurring in stones with hypercalcemic disorders is calcium phosphate, but calcium oxalate may also be present.

Special laboratory studies that have been particularly helpful in the differential diagnosis of hypercalcemic states include roentgenograms of bone and measurement of serum immunoreactive parathyroid hormone. Subperiosteal bone resorption, which is most commonly demonstrated on roentgenograms of the hands with the use of high-quality industrial film, is diagnostic of hyperparathyroidism [11]. The presence of Paget's disease and neoplastic involvement of the bone are other examples in which roentgenograms of bone may be helpful in the differential diagnosis of hypercalcemia. The concentration of serum immunoreactive parathyroid hormone is elevated in hyperparathyroid states, whereas it is commonly low or undetectable in the other metabolic abnormalities associated with hypercalcemia [12,

13]. Stress tests including phosphate deprivation, parathormone infusion, calcium infusion, cortisone suppression, and thiazide administration have been reported to be useful in the differential diagnosis of hypercalcemia [14–19].

Neoplastic disorders are the most common cause of hypercalcemia, yet stone formation is rare. As previously stated, this may be related to the tendency for the hypercalcemia with malignancy to be a late or terminal complication. Primary hyperparathyroidism is the most common hypercalcemic state associated with calcium urolithiasis. Approximately 50% of patients with surgically proven hyperparathyroidism have evidence of stone formation, and approximately 5% of the adult stone formers will have this endocrinopathy. Immobilization, particularly in adolescent patients with active bone formation, may be complicated by hypercalcemia and hypercalciuria, with subsequent formation of stones within the urinary tract. The milk-alkali syndrome and hypervitaminosis D, now rare disorders, can be associated with calcium urolithiasis, nephrocalcinosis, and renal insufficiency. Sarcoidosis with its associated hypersensitivity to vitamin D may produce massive hypercalciuria (greater than 700 mg/24 hr) and hypercalcemia. With all of these disorders, treatment is based on accurate diagnosis of the underlying metabolic disorder and subsequent correction of the hypercalcemia and associated hypercalciuria when possible. With such correction, stone formation within the urinary tract ceases, unless some other cause is present, such as infected urolithiasis, cystinuria, or idiopathic hypercalciuria.

Idiopathic urolithiasis

The syndrome of idiopathic urolithiasis includes various metabolic disorders and is the most common cause of calcium urolithiasis in industrialized countries. This diagnosis is currently applied to perhaps 80% of patients who have formed stones within the urinary tract. It remains a diagnosis of exclusion, made only when all other potential causes of stone formation have been ruled out. Although definable metabolic abnormalities have been described in patients with this syndrome, the underlying mechanisms of these various abnormalities are poorly understood.

Typically, these patients have normal serum concentrations of calcium, low normal or low serum concentrations of phosphorus, and hypercalciuria when on an average calcium intake (in 50 to 75% of patients). Calcium oxalate is the most common crystal found in the stones of these patients, but calcium phosphate (as pure or mixed stones) and uric acid (usually as mixed stones) can be present. This syndrome is more common in males than in females, and the initial presentation of symptoms is usually in the third or fourth decade of life. A family history of stone formation is often present in these patients. Little is known of the patterns of inheritance, primarily because of our lack of knowledge concerning the underlying metabolic abnormalities.

The recognized disturbances of metabolism in patients with idiopathic urolithiasis can be divided into two groups, based on the urinary excretion of calcium. In the first group (50 to 75%), the patients have hypercalciuria on an average calcium intake. These patients can be divided further into those with increased absorption of calcium from the intestine (absorptive hypercalciuria) and those with persistent renal leak of calcium into the urine (renal hypercalciuria). Absorptive hypercalciuria and renal hypercalciuria probably constitute the two major variants of idiopathic hypercalciuria.

An abnormality of calcium absorption from the intestine was first noted by Peacock, Knowles, and Nordin [20]. They showed, in patients with idiopathic urolithiasis and hypercalciuria who had fasted overnight, that the urinary concentration of calcium decreased to within the normal range. More recently, Pak et al [21] have confirmed these observations and devised a simple test for the differential diagnosis of hypercalciuria. They measured, in a group of patients with hypercalciuria, the urinary excretion of calcium, cyclic AMP, and creatinine in a two-hour sample of urine after an overnight fast and in a four-hour sample of urine after administration of 1 g of calcium by mouth. In patients with an absorptive defect in the intestine, the fasting urinary calcium was less than 0.11 mg/mg of urinary creatinine, and it increased to elevated levels after a calcium load (more than 0.2 mg/mg of creatinine). Recent studies of vitamin D metabolism in patients with absorptive hypercalciuria have demonstrated an increase in plasma 1,25-dihydroxy vitamin D, an abnormality that may be related in part to the low serum levels of phosphorus in these patients [22].

Another abnormality associated with hypercalciuria in patients with idiopathic urolithiasis—renal hypercalciuria—was suggested by Coe et al [23]. They found an increased concentration of immunoreactive parathyroid hormone in 26 of 40 patients with idiopathic hypercalciuria, and this returned to normal or nearly normal levels when the hypercalciuria was corrected with the administration of thiazide diuretics. These observations led the authors to suggest that there was a primary renal leak of calcium, with an associated secondary hyperparathy-

roidism. Pak et al [21] found this abnormality in only 10% of the patients they studied with the method of fasting and calcium-loading described above. Peacock et al [20] found no examples of renal hypercalciuria in the patients they studied. The primary mechanism of the renal leak is unknown.

Within the group of patients with idiopathic urolithiasis and hypercalciuria, there may be patients with high normal or slightly elevated serum concentrations of calcium and resorptive hypercalciuria who later prove to have primary hyperparathyroidism. Yendt and Gagne [24], utilizing ionized calcium, were able to show elevated levels of calcium in a group of women who subsequently were shown by surgery to have primary hyperparathyroidism.

The second major group of patients with idiopathic urolithiasis do not have hypercalciuria on an average calcium intake. Abnormalities described in these patients include primary defects of crystal growth and aggregation inhibitors, increased urinary excretion of oxalate (see Dr. Williams's article, this issue), increased alkalinity of the urine, and abnormalities in uric acid metabolism (see Dr. Coe's article, this issue). Although these metabolic abnormalities have been recognized in patients with idiopathic urolithiasis, the underlying causes remain unknown.

Inhibitors of crystal growth and aggregation found in the urine are discussed in detail elsewhere in this symposium (see Dr. Fleisch's article, this issue). Thomas [25] has reported a gross decrease in the low-molecular-weight nonhydrolyzable inhibitors of calcium phosphate crystal growth in patients with active stone formation due to idiopathic urolithiasis. Robertson and Peacock [26] have noted a decrease in the large-molecular-weight inhibitors of calcium oxalate crystal aggregation in stone-formers with recurrent calcium oxalate stones due to idiopathic urolithiasis. Again, the mechanisms of these deficiencies are unknown.

Robertson, Peacock, and Nordin [27] reported two groups of patients with idiopathic urolithiasis without hypercalciuria. The first group were forming calcium oxalate stones and had mild increases in the urinary excretion of oxalate without increases in excretion of glycolate or L-glyceric acid. The second group were forming calcium phosphate stones and had persistently alkaline urine while eating their normal diet, yet they had no renal abnormality in terms of acid-handling. Their response to an ammonium chloride load was normal. Again, the underlying mechanisms of these abnormalities are unknown.

Coe and Kavalach [28] have suggested an additional abnormality in patients with idiopathic urolithiasis, namely normocalciuria and recurrent calcium oxalate stones. They have found a persistent elevation of the urinary excretion of uric acid in some of these patients without hyperuricemia. Based on the observations of Lonsdale [29] on the close dimensional similarity of many of the crystal phases of the common crystalline components of urinary calculi, they suggested that the uric acid or sodium acid urate crystals could form spontaneously in this setting and induce nucleation of calcium oxalate by the mechanism of epitaxy. Once the calcium oxalate crystals had formed, they could aggregate and grow in patients with idiopathic urolithiasis when the state of saturation was metastable for calcium oxalate. This mechanism is reviewed in more detail elsewhere in the symposium (see Dr. Coe's article, this issue). A recent study by Robertson et al [30] reported that the urinary saturation of uric acid, sodium urate, and ammonium urate was below the formation product in all but two of their patients with idiopathic urolithiasis and calcium oxalate stone formation. For spontaneous uric acid crystal formation to occur, it is a prerequisite for the epitaxy theory that uric acid saturation be above the formation product at which spontaneous nucleation of crystals would occur.

Current therapy of idiopathic urolithiasis, which is discussed in detail elsewhere in the symposium, is directed toward correcting the abnormalities described above. Perhaps in none of the many metabolic disorders associated with urolithiasis is the concept of metabolic activity more important than in idiopathic urolithiasis. Stone formation is often variable between patients and within the same patient.

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